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Douxfils, Jonathan; Chatelain, Bernard; Dogné, Jean-Michel; Mullier, François

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Real-world variability in dabigatran levels in patients with atrial fibrillation: comment

Authors and affiliations:

Jonathan Douxfils[1], Bernard Chatelain[2], Jean-Michel Dogné[1], François Mullier[2]

[1] Department of Pharmacy, Namur Thrombosis and Hemostasis Center (NTHC), Namur Research Institute for LIfe Sciences (NARILIS), University of Namur, Belgium

[2] Hematology Laboratory, Namur Thrombosis and Hemostasis Center (NTHC), Namur Research Institute for LIfe Sciences (NARILIS), CHU DinantGodinne UcL Namur, Université Catholique de Louvain, Belgium

Corresponding author:

Jonathan Douxfils, Department of Pharmacy, Namur Thrombosis and Hemostasis Center (NTHC), Namur Research Institute for LIfe Sciences (NARILIS)

Faculty of Medicine, University of Namur

61, rue de Bruxelles, B-5000 Namur, Belgique

jonathan.douxfils@unamur.be

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We read with interest the recent prospective observational study by Chan *et al.*[1] The authors aimed to investigate the inter- and intra-patient variability in dabigatran plasma levels with the 110 and 150 mg *bid* dose regimens in 100 patients suffering from atrial fibrillation (AF). They also assessed the effect of physicians' dose selection on plasma levels in the two different subgroups and explored whether a single trough measurement would identify patients with extreme plasma levels on subsequent visits, i.e. at 2-, 4- and 6-months [1]. They support the practice of selecting dabigatran dose based upon clinical characteristics because it results in similar levels of drug exposure in patients given the 110 or the 150 mg *bid* dose regimen. However, they do not support the concept that a single plasma level measurement with the Hemoclot Thrombin Inhibitor® (Hyphen BioMed) can be used to identify patients with consistently high or low plasma levels.

In their study, Chan *et al.* revealed an impressive 17-fold variation in plasma concentrations (from ≤ 30 ng/mL to 510 ng/mL) at trough (i.e. at a median of 13.3 ± 4.7 hours after the last drug intake) with an inter-patient geometric coefficient of variation (gCV) of 63.8%. This variation was equally important when plasma level was assessed at peak (i.e. at a median of 2.5 ± 0.2 hours after the drug intake) with an inter-patient gCV of 50.9%. They mention that the ranges of plasma levels were similar at baseline, 2-, 4- and 6-months. The greater variability observed at C_{trough} is questionable as our study and another showed lower variability in samples taken at trough [2, 3]. The variability of the median delay since the last drug intake is more important for blood taken at trough (4.7 hours) than at peak (0.2 hours) which certainly explains an important part of this discrepancy. Consequently, this is a major limitation that prevents firm conclusions.

Results of the intra-individual variability are even more equivoque. They founded gCVs of 32.9% and 39.5% for trough and peak levels, respectively. Based on the 100 patients screened at baseline, they defined the upper 20^{th} centiles (n=20 patients) as equal to 129 ng/mL. Trough plasma levels remained above that threshold in 88.2%, 80.0% and 70.0% of patients at the 2-, 4- and 6-months visit, respectively. Similar analyses were performed for the upper 10^{th} centiles (plasma level of 180 ng/mL and n=10 patients) as well as in the lower 20^{th} centiles (plasma level of 38 ng/mL and n=20 patients). Based on these results, they mention that "*over the 6 months measurement of drug concentrations, up to 40% of patients whose baseline trough level were in*

the upper 20th and 10th centiles has subsequent levels that no longer fell within these respective extremes and that an even higher proportion (up to 80%) of patients with a single low trough measurement did not have subsequent level in the low extreme." They conclude that "*these findings highlight the limitation of a single Hemoclot® measurement in reliably identifying patients with extreme drug levels*". We believe that their conclusions should be interpreted more cautiously for the following reasons. First, the lack of individual data precludes firm conclusion regarding the concept of a single Hemoclot Thrombin Inhibitor® measurement. Namely, one cannot assert if it was the same patients that no longer fell within these respective extremes. In addition, from the 20 patients identified upon the threshold of 129 ng/mL (the 20th centiles at baseline), data at 2-, 4- and 6-months were only available for 17, 10 and 10 patients, respectively. That 50% of patients were not included at all stages of follow-up is clearly a limitation, as outlined by the authors [1]. More importantly, for trough plasma data, the median value of the delay since the last drug intake had an impressive variation of ± 4.7 hours. Thus, a patient initially identified above the threshold of 129 ng/ml can be normalized due to the fact that the delay since the last intake is more important at the 2-, 4- or 6-months visit. A previous simulated pharmacokinetic analysis from the RE-LY study stipulated that a 6-hour delay might put trough level outside the variability of a typical AF patient [2]. For the 20th lower centiles, the authors acknowledged that the test used has a limit of quantitation (LOQ) of 30 ng/mL. Our recent study demonstrated that for concentration ≤ 30 ng/mL it is certainly more appropriate to use a test dedicated to measure these low levels and probably not only < 30 ng/mL [3]. Moreover, other pre-analytical and analytical laboratory key information is still lacking and are not discussed here as a possible limitation. For example, there is no mention of the stability of dabigatran plasma sample at -80°C and its impact on the Hemoclot Thrombin Inhibitor® assay. If the analyses were performed within the same run, it is possible that the plasma collected 6 months, or more, before the experiment does not react similarly than a sample collected 2 months before the analysis. In addition, the authors failed to mention if different batches of the Hemoclot Thrombin Inhibitor® assay have been used and the delay between the blood sampling and the congelation is not stated.

Furthermore, it would have been very interesting to obtain data on clinical outcomes as well as on the reason(s) for the 6 treatment cessations. However, and interestingly, Chan *et al.* found that dose adaptation based on the patients' clinical characteristics (mainly age and renal clearance)

results in similar median trough and peak level. This confirms the choice of the different regulatory agencies to adopt the lower dose for patients with factors for drug accumulation [4-6].

In conclusion, the above limitations clearly highlight that the conclusions of Chan *et al.* probably need to be toned down. As previously mentioned, several criteria should be taken into consideration when considering proper drug monitoring: a high (A) intra- and (B) inter-individual variability in drug level, both justifying identification of the optimal dose for each patient at the start of treatment; (C) a low variability and good reproducibility in the assay method; (D) a correlation between drug level and clinical event and (E) the demonstration of the value of the therapeutic drug monitoring [7]. Up to now, the high intra- and inter-individual variability in drug level is clearly demonstrated [8] and the results from Chan *et al.* support this observation. Techniques for plasmatic drug measurements are evolving, suggesting that with appropriate methods, one can accurately assess the therapeutic response [3, 9-13]. The correlation between the drug level and the clinical event tends to be demonstrated [8], even if some criticisms have been raised [14], showing that further effort can also be made by assessing the plasma concentration at the time of the outcome. As mentioned above, delay since the last intake of the drug and the blood sampling is mandatory and strict protocols are needed to accurately investigate this. Therefore, a well-designed study, assessing the plasma level with adequate coagulation tests and restricting the delay since the last drug intake for the trough measurement at 12 hours ± max 1 hour, is still required to provide accurate recommendations on the usefulness of a single measurement to identify high or low responders.

Jonathan Douxfils[1], Bernard Chatelain[2], Jean-Michel Dogné[1], François Mullier[2]

Conflict of interest

F. Mullier reports advisory board status from Sanofi-Aventis and from Bristol-Meyers Squibb outside the submitted work. The other authors state that they have no conflict of interest.

Addendum

J. Douxfils, B. Chatelain, F. Mullier and J.-M. Dogné were the main investigators of the manuscript.

J. Douxfils wrote the first draft of the manuscript and the final version.

B. Chatelain, J.-M. Dogné and F. Mullier were responsible of the review of the manuscript.

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